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Declines in Human Papillomavirus (HPV) – Associated High-Grade Cervical Neoplasia by Sociodemographic Factors After Introduction of HPV Vaccines in Connecticut, USA 2008-2017

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Conflicts of Interest

Linda Niccolai, PhD has served as a scientific advisor for Merck. Daniel Weinberger, PhD has received consultation fees from Pfizer, GSK, and Affinivax. All other research collaborators report no conflicts of interest.

Keywords: Human Papillomavirus, HPV, cervical lesions, surveillance, HPV vaccine

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Short Summary

Since the approval of the HPV vaccine by the FDA in June 2006, there have been statistically significant declines in diagnoses of high grade cervical intraepithelial neoplasia in women ages 21-24 in the state of Connecticut across race, ethnicity, and socioeconomic status with respect to the federal poverty line. This downward trend remains statistically significant across all three sociodemographic factors in women ages 21-24 after adjusting incidence rates to account for only women who have undergone cervical pap smears.

Table of Contents

Abstract

Background: In 2006, the FDA approved the first vaccine against human papillomavirus. Trends in HPV-related sequalae are an effective method of analyzing HPV vaccine impact. Our primary objective was to measure trends in cervical neoplasia based on sociodemographic characteristics including race, ethnicity, and socioeconomic status.

Methods: Since 2008, Connecticut has required reporting of cervical intraepithelial neoplasia labeled grade 2+ and adenocarcinoma in situ. CIN 2+ diagnoses trends were modeled by area-based measures of age, race, ethnicity, and socioeconomic status using negative binomial regression and change-point analysis. Incidence rate measurements were adjusted to reflect inclusion of women who had completed cervical pap smears.

Results: From 2008-2017 incidence rate of cervical intraepithelial neoplasia per 100,000 person-years declined by 65-85% in 21-26-year-old women. After adjusting by BRFSS data incidence rate declines only remain significant in women ages 21-25 with diagnoses dropping from 30-80%. Significant declines were demonstrated across sociodemographic factors. Women ages 21-24 showed significant declines in CIN 2+ regardless of what percentage of the population in their census tract identified as Black, Latino, or below the federal poverty line. From 2008-2017 the incidence rate of cervical intraepithelial neoplasia per 100,000 person-years declined by 73-76% across all census tracts, regardless of what percentage of the population in their census tract identified as Latino (i.e. less than 5%, 5-10%, 10-20%, and greater than 20%). For area-based measures of racially identifying as Black the decline was 75-77%. Lastly, for area-based measures of identifying as below the federal poverty line the decline was 71-78%. When data was adjusted for screening population using BRFSS data the results were as follows: 66-69% decline in incidence rate of CIN 2+ across area-based measures of racially identifying as Black, 63-68%

decline in incidence rate across area-based measures of identifying as Latino, and 62-70% decline in incidence rate across area-based measures of identifying as below the federal poverty line.

Conclusions: Significant declines in CIN+2 diagnoses from 2008-2017 were observed in the overall population and amongst the estimated screened population. These trends are suggestive of declines attributable to HPV vaccination in CT. The significant decline in incidence across different sociodemographic factors, even after stratifying census tracts by the portion of their populations that identify as Black, Latinx, or below the federal poverty line (FPL) demonstrates that vaccine impact is reaching various sociodemographic groups and reduces risk of results confounding by race, ethnicity, and socioeconomic status.

Introduction

In 2006, the Federal Drug Administration (FDA) approved a quadrivalent HPV vaccine developed for girls aged 9 to 26. The vaccine provided immunity against the four most common HPV strains, 6, 11, 16 and 18[1]. Approximately 66% of cervical cancer cases are attributable to HPV-16 & HPV-18[2]. HPV-6 and HPV-11 are responsible for over 90% of anogenital warts cases[2]. The CDC's Advisory Committee on Immunization Practices (ACIP) recommends administration of the HPV vaccine to all young girls ages 11-12 and catch up vaccination schedules for girls ages 13-26[3]. The vaccine was initially administered in 3 doses over a 6-month time period.

The HPV vaccine has been modified in content and implementation efforts since initial approval in 2006. In 2009 the vaccine was approved for use in boys ages 9-26 to provide immunity against HPV related sequalae such as anogenital warts and anal & penile cancers. This change in FDA approval was followed by recommendations from the ACIP in 2011 to vaccinate all boys ages 11-12 and perform catch up vaccination schedules in boys ages 13-21. In 2014 the vaccine was changed to a nonvalent format providing additional coverage against HPV strains 31, 33, 45,

52, and 58[3]. In 2016 clinical guidelines were changed to recommend a 2-dose schedule for all youth ages 9-14. In October 2018 the FDA approved use of the HPV vaccine for immunization of all men and women ages 27-45[3]. However, this approval is not currently supported by ACIP recommendations. There is growing interest in researching the impact of HPV vaccination on HPV related sequalae including incidence of anogenital warts, precancerous lesions, and cancer diagnoses[4,5].

The Connecticut Emerging Infections Program, a collaboration between the Connecticut Department of Public Health and the Yale School of Public Health, has engaged in active, population-based surveillance of HPV pre-cancerous cervical lesions since 2008 [6]. The decision was made to support efforts from the Centers for Disease Control & Prevention (CDC) to monitor the impact of HPV vaccination uptake on HPV related sequelae. The efforts of EIP reflect similar endeavors performed elsewhere in the United States [7,8], Australia [9,10,11], Canada[12], and Denmark[13].

In 2008 the Connecticut Department of Public Health began requiring reporting of all cervical intraepithelial lesions grade 2 or higher and adenocarcinoma in situ (collectively referred to as CIN 2+) to ensure complete case ascertainment. Over the past several years, HPV-IMPACT has identified temporal trends in CIN 2+ incidence to assess the impact of the HPV vaccine and compared these changes with shifts in sexual behavior, STI prevalence, and frequency of Pap smear screenings [6]. The latter is of particular importance due to recent changes in cervical cancer screening clinical guidelines. Prior to 2012, clinical guidelines from the U.S. Preventive Services Task Force (USPSTF) recommended that women ages 21-29 undergo annual Pap smears. After 2012, women ages 21-29 were recommended cytology (Pap smear) testing alone every 3 years (instead of annually). Women ages 30-65 were given the same recommendation and additionally offered the alternative recommendation of cytology and HPV testing every 5 years [14]. As of 2018,

clinical guidelines have changed again. New recommendations provide women ages 30-65 with three options. They can engage in cytology testing alone every 3 years, high risk HPV testing alone every 5 years, or cytology testing in conjunction with high risk HPV testing every 5 years [15]. The 2012 change from recommending Pap smears annually to triennially may risk confounding declines in diagnoses of CIN 2+ lesions by conflating decreased screening and detection.

Current surveillance analyses have regularly focused on age and birth cohorts [6]. Recent literature demonstrates associations showing that younger women in age groups 14-19 and 20-24 has seen declines in HPV related sequalae, including intraepithelial cervical neoplasia grade 2+ and anogenital warts, in the years after FDA approval of the HPV vaccine in the United States[8,9]. Missing from current literature are statistical analyses demonstrating CIN 2+ incidence declines in racial/ethnic groups and women in low socioeconomic brackets. This information is critical because data shows that as recently as 2017, racial minorities continue to have higher incidence rates of cervical cancer diagnoses & cervical cancer related mortality [16.] A sociodemographic analysis of incidence rate trends can help identify if vaccine access and population immunity is a homogenous phenomenon or if remaining incident cases are clustering around certain sociodemographic groups as a result of heterogenous vaccine distribution or utilization. Additionally, we expand upon the previous work of Niccolai et al. (2017) by extending the age-based time series analysis of CIN 2+ incidence trends up until 2017 and by performing time series analyses of CIN 2+ incidence trends from 2008-2017 across race, ethnicity, and socioeconomic status.

Methods

The Emerging Infections Program has been collecting data on cervical intraepithelial neoplasia (CIN) since 2008 in conjunction with the Department of Public Health (DPH) of

Connecticut. Women who identified under the age of 21 were excluded from this analysis due to changes in clinical guidelines in 2012 which now recommend that women under age 21 do not undergo routine cervical cancer screening. Population denominators used to calculate incidence rates were obtained through two different sources – the U.S. Census Bureau American Community Survey (ACS) and the Behavioral Risk Factor Surveillance System (BRFSS).

The American Community Survey identified 411,624 women in Connecticut between the ages of 21-39. Incidence rates were calculated by dividing case counts by the total population of women in CT who identify between the ages of 21-39. To account for the fact that cervical cancer screening is a prerequisite for CIN 2+ diagnosis, the ACS denominators were adjusted by multiplier values using data from BRFSS. This allowed incidence rate calculations to only include women who have undergone cervical cancer screenings. BRFSS multiplier values were calculated for each year by dividing the number of women who self-reported as having a Pap smear in the past year by the total number of women. Women who expressed uncertainty when asked if they had a Pap smear in the past year were excluded to avoid unintentional distortions of the numerator or denominator values when calculating the population adjustment multiplier value. BRFSS data was only collected biannually. For years without adjustment proportions, multiplier values were obtained by calculating the average of the multiplier value from the preceding and succeeding years.

Change point analyses using negative binomial regressions were performed to identify best-fit models for CIN 2+ incidence rate trends stratified by race, ethnicity, and socioeconomic status. Using U.S. census tract data for all 833 CT census tracts, CIN 2+ cases were counted and categorized by the following categories: census tracts where the percentage of people who identify as Black, Latino/Hispanic, or below the Federal Poverty Line (FPL) compose <5 % of the census

tract population, ≥ 5 % but < 10%, ≥ 10% but < 20%, and ≥ 20%. Trends in declines were visualized by modeling both incidence rates (IRs) and incidence rate ratios (IRRs). Incidence rate ratio values were calculated by using the incidence rate during the first year of follow-up (i.e. 2008) as the reference value. Trends across sociodemographic factors by individual year could not be identified because the sample size in each category would decrease substantially, thereby sharply reducing power and allowing increased risk of type II error in the analysis. In order to maintain substantial power, trends were categorized into age groups with separate models run for age groups 21-24, 25-29, 30-34, and 35-39.

Changes in incidence of cervical neoplasia were tracked annually to account for HPV vaccine impact, both directly and indirectly (i.e. herd immunity). Change-point models were used to identify if declines in CIN 2+ incidence varied by age group in either year of onset or rate of decline. Change-point analyses were created using negative binomial regression models. The outcome of interest for each model was the incidence rate of CIN 2+ per 100,000 person-years for each age group. An alternative regression model was fit for each year during which data were collected (10 models total). These models included intercept-only models and models that demonstrated steady linear declines in CIN+2 incidence rates from 2008-2017 after undergoing log transformations. Optimal change-point models were identified by weights generated from Akaike criterion scores. Higher weights were allocated to better fitting models. Akaike scores estimate the quality of models used in statistical analysis while accounting for risks of underfitting (i.e. too simplistic) and overfitting (i.e. too many parameters) of models.

Results

Between 2008-2017 there were 17,605 cases of cervical intraepithelial neoplasia diagnosed as grade 2 or higher. Annual incidence declined from 2,117 cases in 2008 to 1,320 cases in 2017 (see Figure 1).

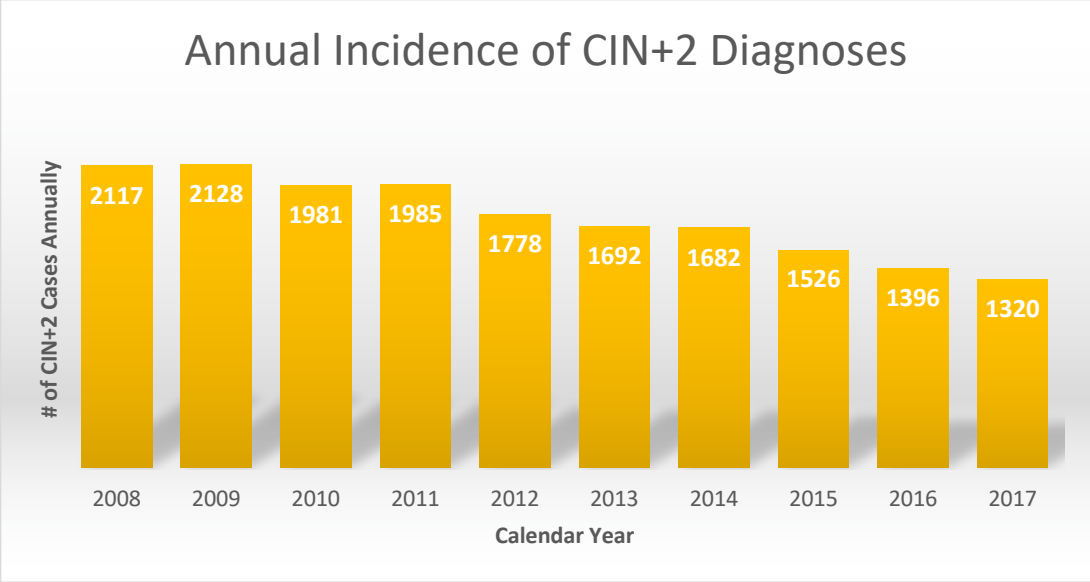


Figure 1: Annual Incidence Count of CIN 2+ Diagnoses in Connecticut

When U.S. census tract data was used to stratify CIN 2+ incidence rate ratio trends by race, ethnicity, and socioeconomic status, statistically significant declines were observed in individuals ages 21-24. This held true across all categories of census tract populations identifying as Black (see figure 2), census tract populations identifying as Hispanic (see figure 3), and census tract populations identifying as below the federal poverty line (i.e. < 5%, between 5 and 10%, between 10% and 20%, and greater than 20%) (see figure 4). Incidence rate declines were also observed in age groups 25-29, 30-34, and 35-39. However, unlike in the 21-24-year age group, declines were not consistent across all census tract categories. In fact, incidence rate increases were observed across census tracts where more than 10% of individuals identify as Black, Latinx, or below the FPL. However, these trends were not shown to be statistically significant since the 95%

confidence intervals for incidence rate ratios included the null value of 1.00. Statistically significant declines were also observed in age group 21-24 across race, ethnicity, and socioeconomic status when incidence rate ratios were estimated among screened women. Similarly, when analysis was adjusted by BRFSS data the trends observed and predicted for incidence rates of CIN 2+ in age groups 25-29, 30-34, and 35-39 was found not to be statistically significant since 95% confidence intervals included the null value of 1.00 (see figures 5-7).

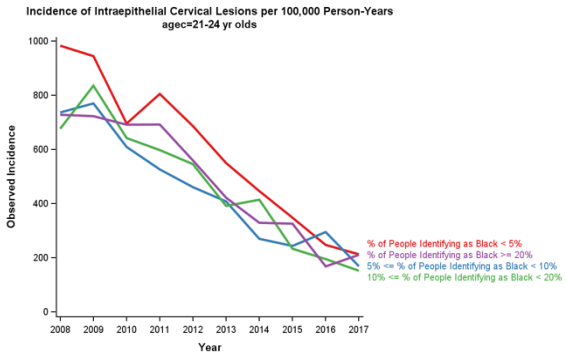
Table 1: CIN+2 IRR Trends – Total Population Demographics - U.S. Census Tract Data

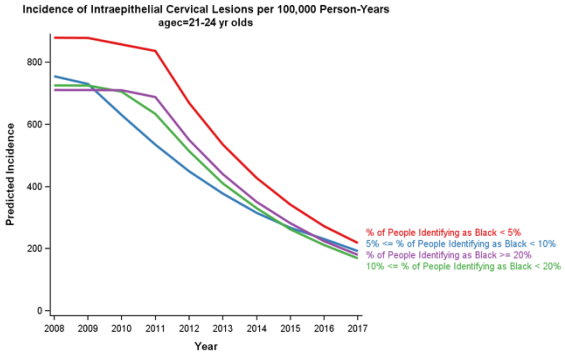
Age Group (21-24-Year-Olds)	% Population Identifying as Black	IRR Decline After 10 Years	IRR Decline 95% Confidence Interval Lower Limit	IRR Decline 95% Confidence Interval Upper Limit
	< 5%	76%	67%	82%
	≤ 5% but < 10%	75%	66%	81%
	≤ 10% but < 20%	77%	64%	85%
	≤ 20%	75%	67%	81%

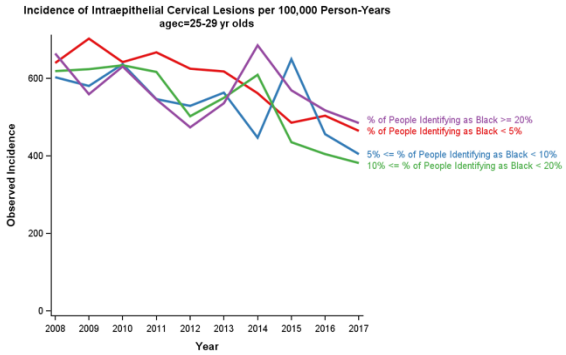
Age Group (21-24-Year-Olds)	% Population Identifying as Hispanic	IRR Decline After 10 Years	IRR Decline 95% Confidence Interval Lower Limit	IRR Decline 95% Confidence Interval Upper Limit
	< 5%	75%	63%	83%
	≤ 5% but < 10%	76%	65%	84%
	≤ 10% but < 20%	76%	68%	82%
	≤ 20%	73%	66%	78%

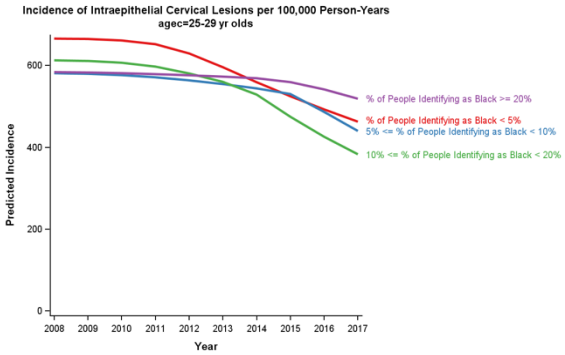
Age Group (21-24-Year-Olds)	% Population Identifying as Below FPL	IRR Decline After 10 Years	IRR Decline 95% Confidence Interval Lower Limit	IRR Decline 95% Confidence Interval Upper Limit
	< 5%	76%	71%	80%
	≤ 5% but < 10%	77%	69%	83%
	≤ 10% but < 20%	71%	64%	77%
	≤ 20%	78%	70%	84%

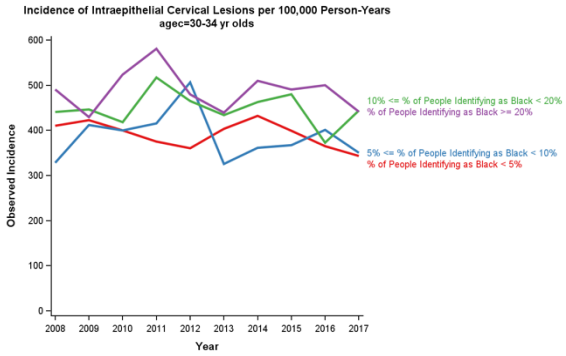
Figure 2: CIN 2+ Incidence Rate Trends – % Population Black – Total Population

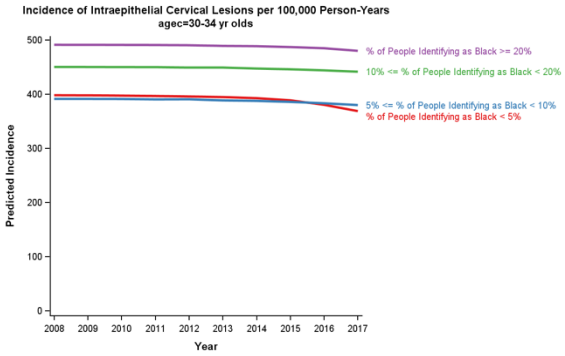


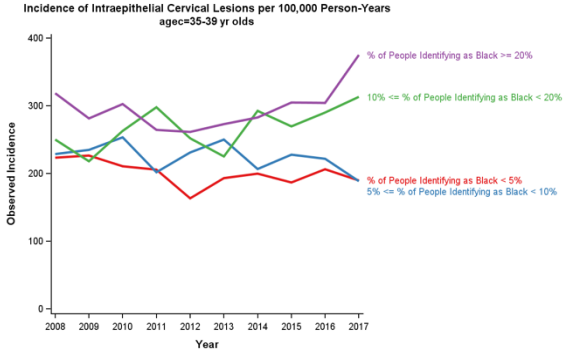












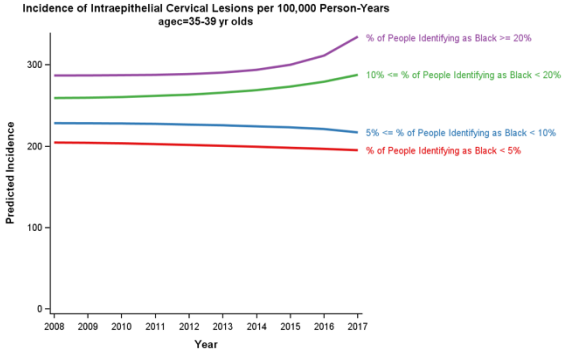
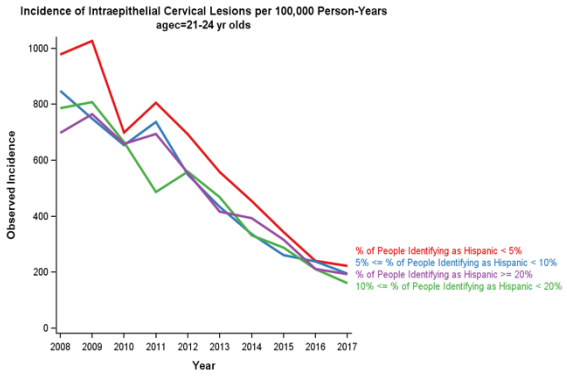
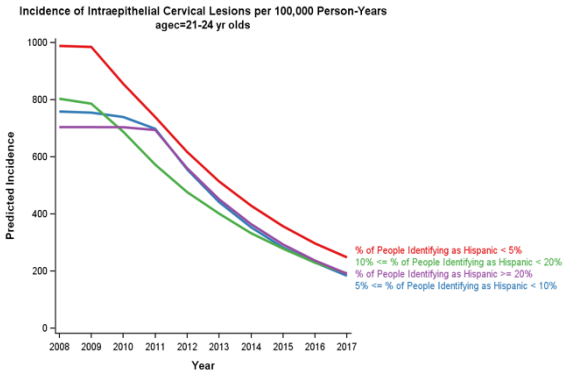
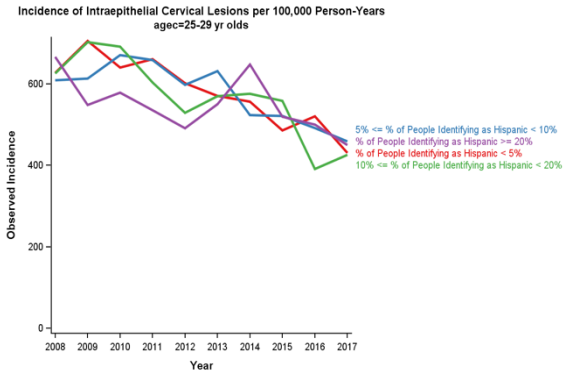
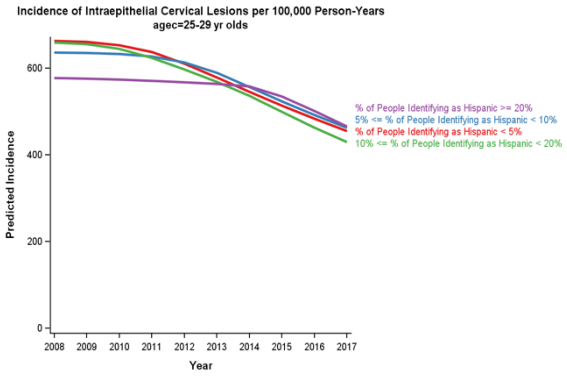


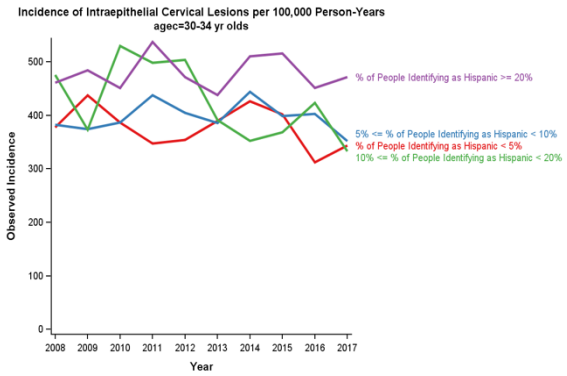
Figure 3: CIN 2+ Incidence Rate Trends – % Population Hispanic/Latino. – Total Population

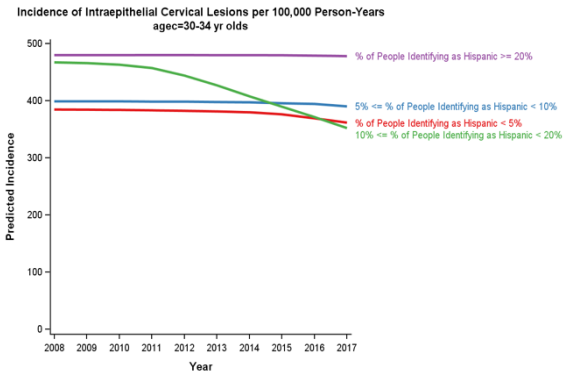


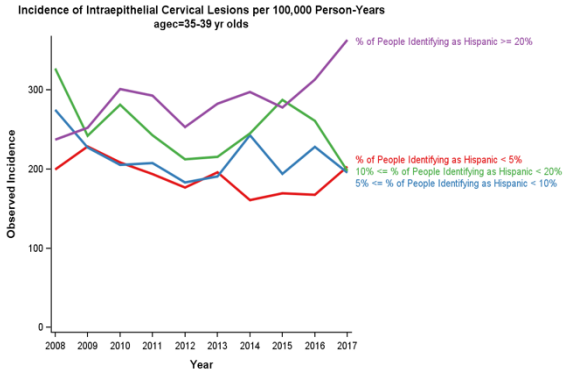












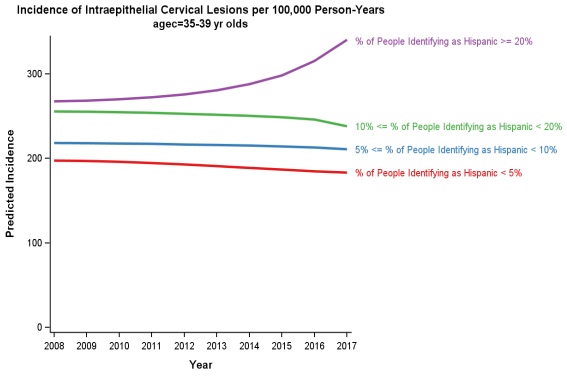
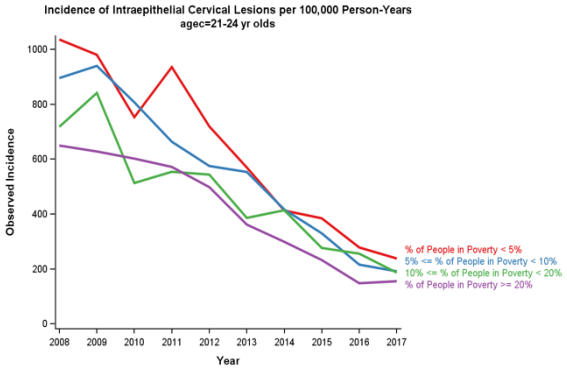
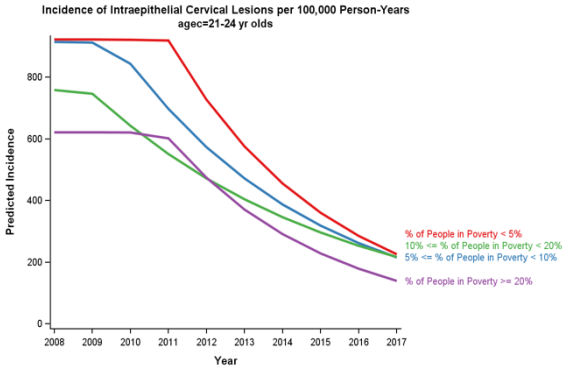
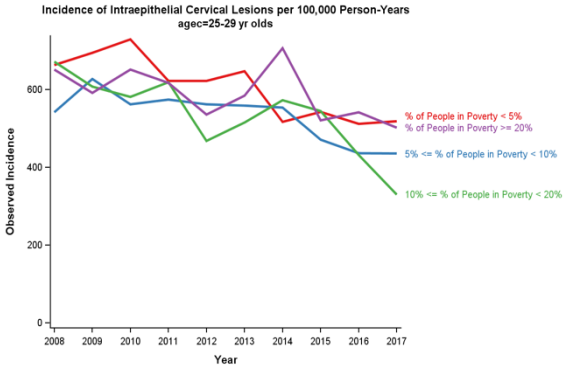
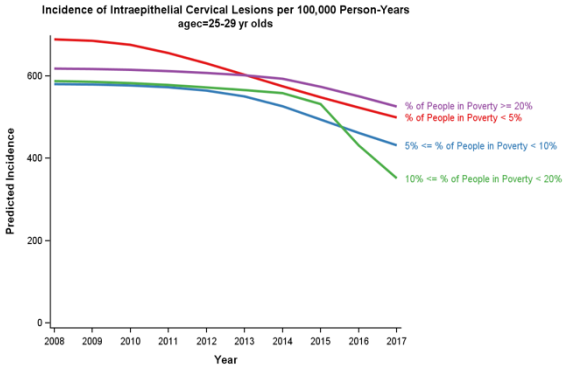


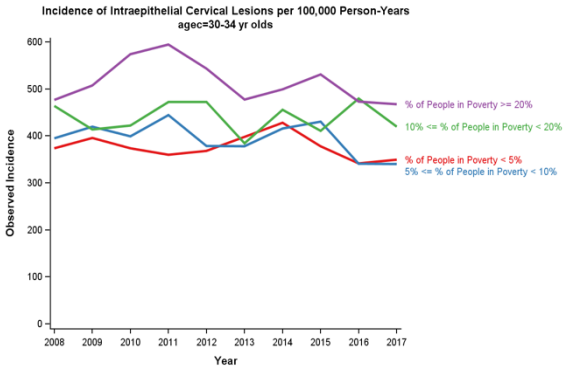
Figure 4: CIN 2+ Incidence Rate Trends – % Population Below FPL – Total Population

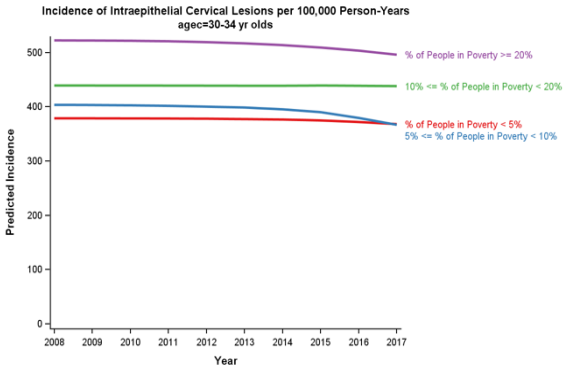


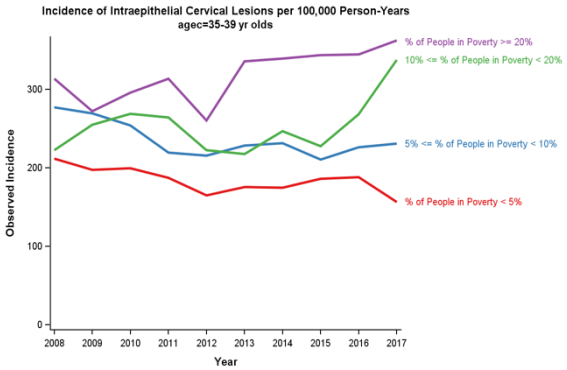












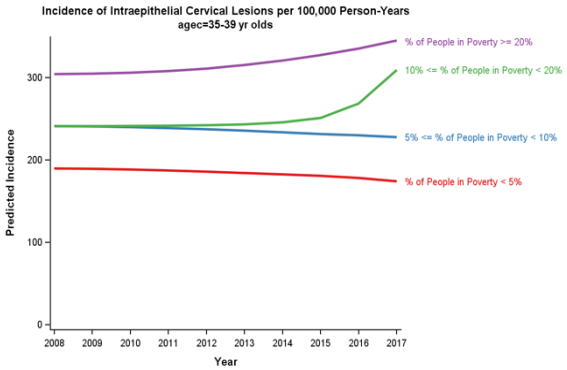


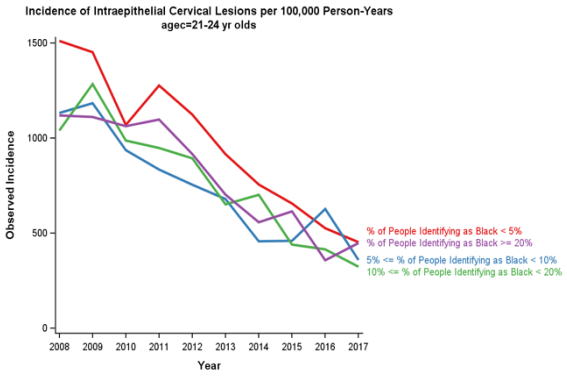
Table 2: CIN +2 IRR Trends – Screening Population Demographics – BRFSS Data

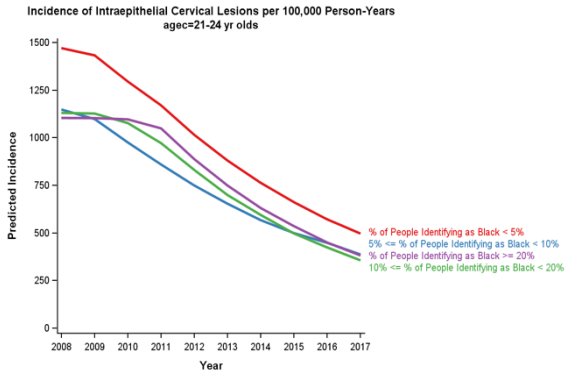
Age Group (21-24-Year-Olds)	% Population Identifying as Black	IRR Decline After 10 Years	IRR Decline 95% Confidence Interval Lower Limit	IRR Decline 95% Confidence Interval Upper Limit
	< 5%	67%	53%	77%
	≤ 5% but < 10%	66%	55%	75%
	≤ 10% but < 20%	69%	52%	80%
	≤ 20%	66%	54%	75%

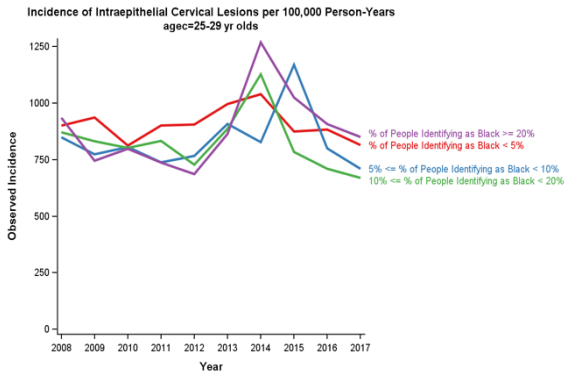
Age Group (21-24-Year-Olds)	% Population Identifying as Hispanic	IRR Decline After 10 Years	IRR Decline 95% Confidence Interval Lower Limit	IRR Decline 95% Confidence Interval Upper Limit
	< 5%	67%	60%	72%
	≤ 5% but < 10%	68%	52%	79%
	≤ 10% but < 20%	68%	57%	76%
	≤ 20%	63%	53%	71%

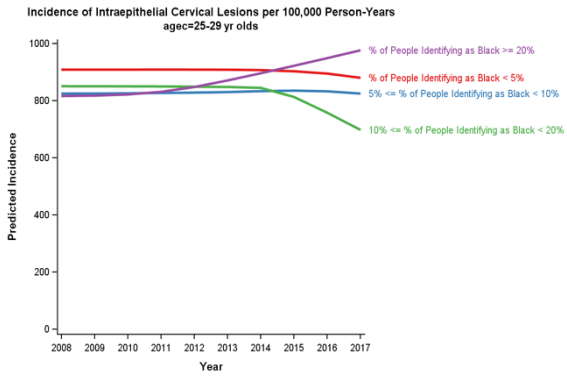
Age Group (21-24-Year-Olds)	% Population Identifying as Below FPL	IRR Decline After 10 Years	IRR Decline 95% Confidence Interval Lower Limit	IRR Decline 95% Confidence Interval Upper Limit
	< 5%	67%	56%	75%
	≤ 5% but < 10%	69%	59%	76%
	≤ 10% but < 20%	62%	52%	69%
	≤ 20%	70%	58%	79%

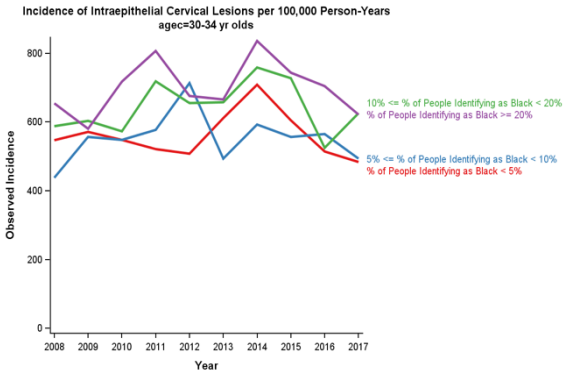
Figure 5: CIN 2+ Incidence Rate Trends – % Population Black – Screening Population

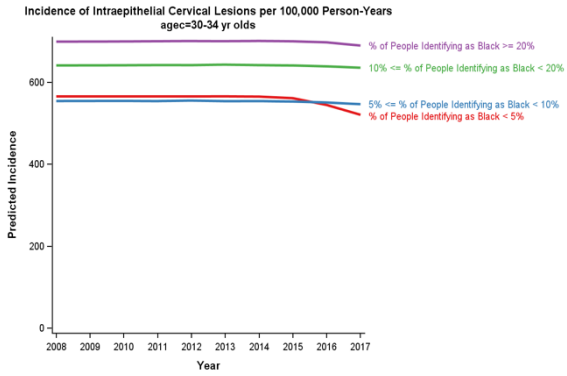


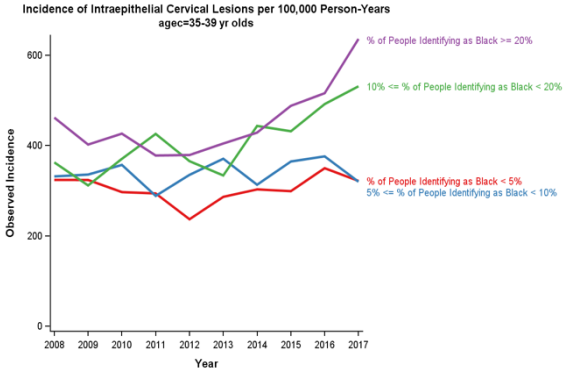












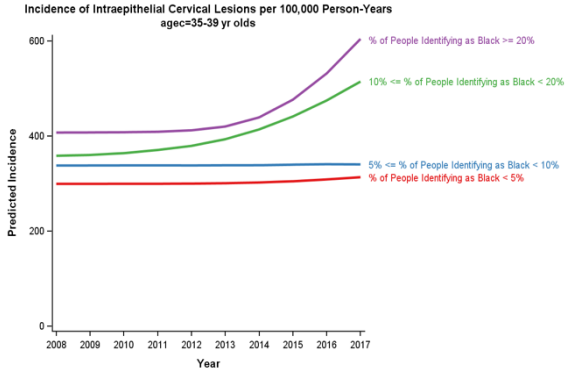
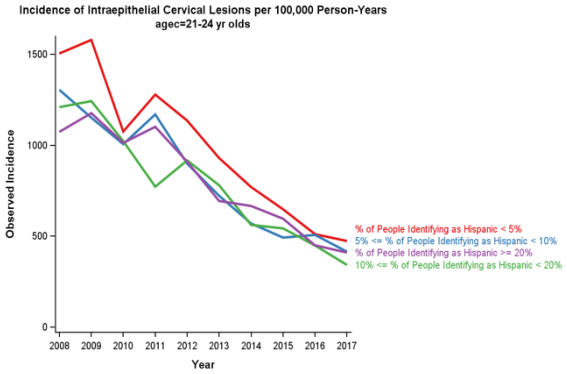
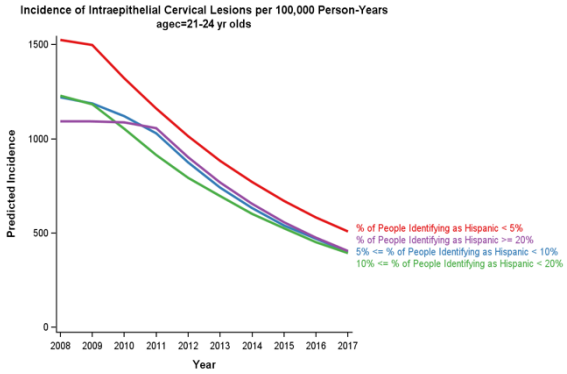
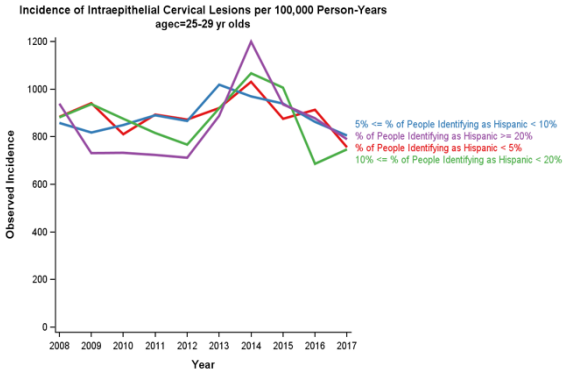
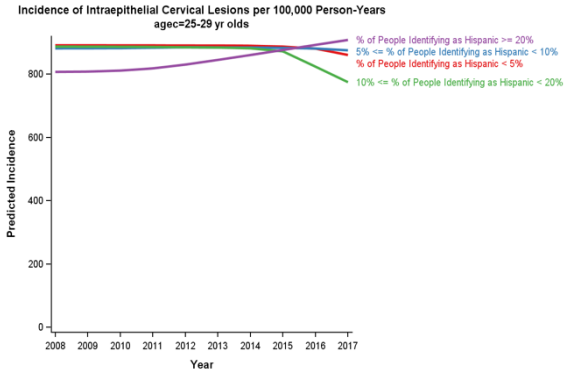


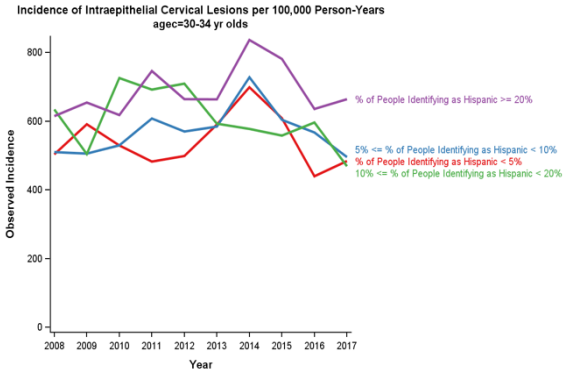
Figure 6: CIN 2+ Incidence Rate Trends – % Population Latino/Hispanic – Screening Population

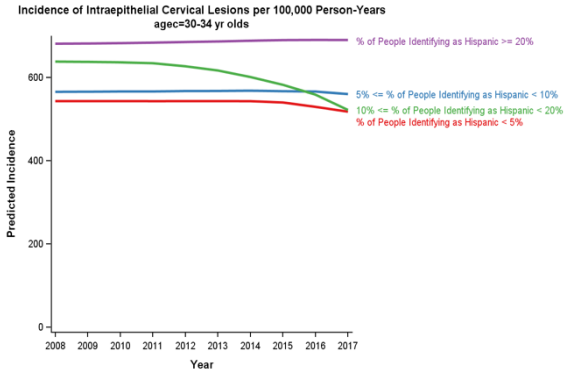


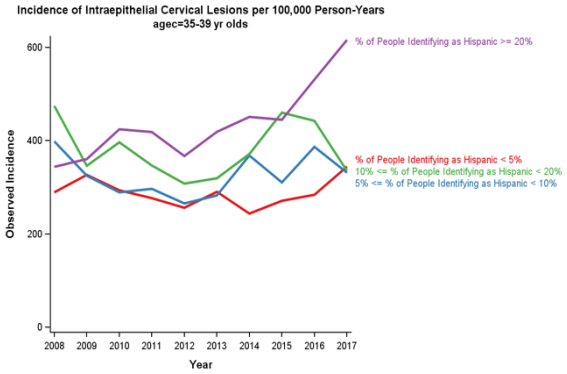












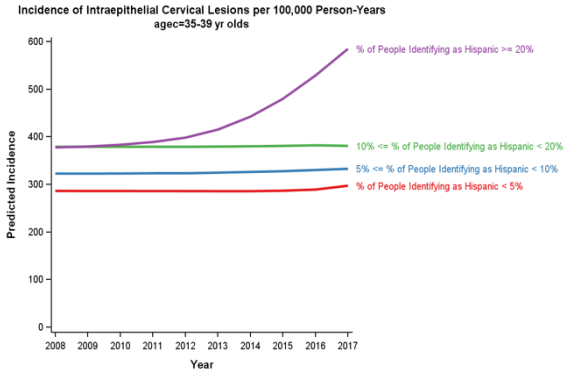
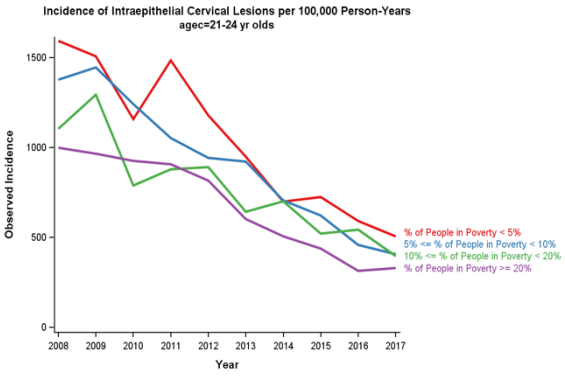
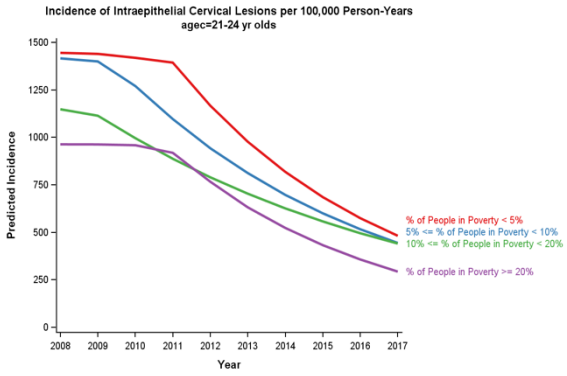
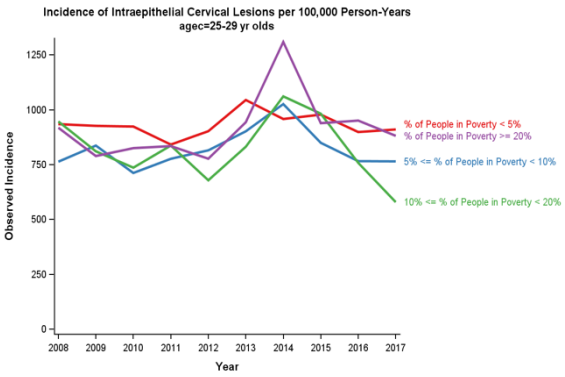
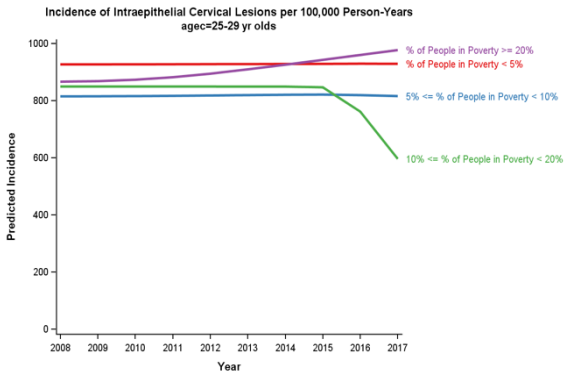


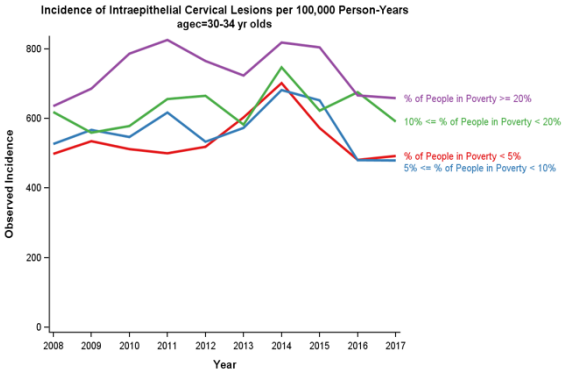
Figure 7: CIN 2+ Incidence Rate Trends – % Population Below FPL. – Screening Population

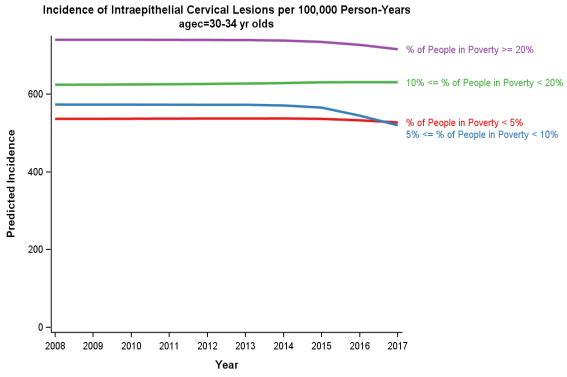


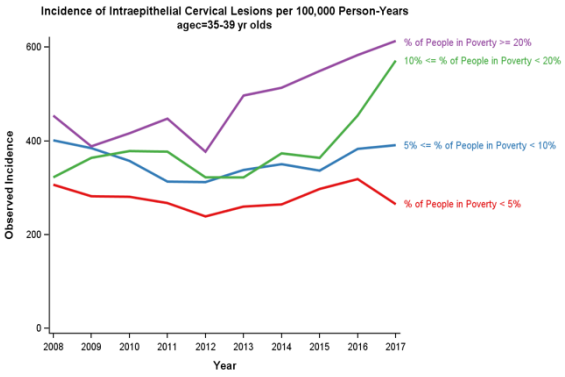


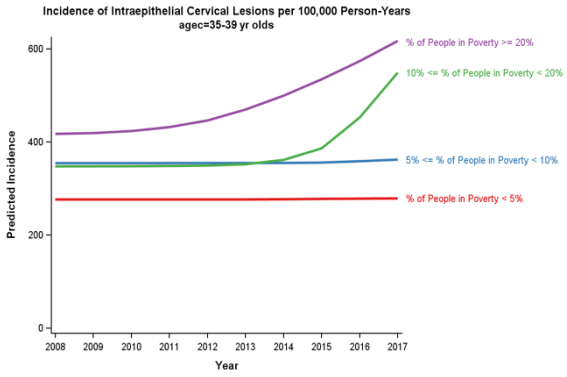












When using total population, significant declines in CIN 2+ incidence rate ratios were found in women ages 21-24 across all area based measures of sociodemographic characteristics: % census tract population identifying as Black < 5% [76% decline in IRR, 95% CI (67%, 82%)], % census tract population identifying as Black between 5% and 10% [75% decline in IRR, 95% CI (66%, 81%)], % census tract population identifying as Black between 10% and 20% [77% decline in IRR, 95% CI (64%, 85%)], % census tract population identifying as Black greater than 20% [75% decline in IRR, 95% CI (67%, 81%)]. % census tract population identifying as Hispanic < 5% [75% decline in IRR, 95% CI (63%, 83%)], % census tract population identifying as Hispanic between 5% and 10% [76% decline in IRR, 95% CI (65%, 84%)], % census tract population identifying as Hispanic between 10% and 20% [76% decline in IRR, 95% CI (68%, 82%)], % census tract population identifying as Hispanic greater than 20% [73% decline in IRR, 95% CI (66%, 78%)]. % census tract population identifying as below the FPL < 5% [76% decline in IRR, 95% CI (71%, 80%)], % census tract population identifying as below the FPL between 5% and 10% [77% decline in IRR, 95% CI (69%, 83%)], % census tract population identifying as below the FPL between 10% and 20% [71% decline in IRR, 95% CI (64%, 77%)], % census tract population identifying as below the FPL greater than 20% [78% decline in IRR, 95% CI (70%, 84%)]. Changes in incidence rate ratios for individuals who identify between the ages of 27-39 were not statistically significant.

When using adjusted BRFSS data, significant declines in CIN +2 incidence rate ratios were found in women ages 21-24 across all sociodemographic characteristics: % census tract population identifying as Black < 5% [67% decline in IRR, 95% CI (53%, 77%)], % census tract population identifying as Black between 5% and 10% [66% decline in IRR, 95% CI (55%, 75%)], % census tract population identifying as Black between 10% and 20% [69% decline in IRR, 95% CI (52%,

80%)], % census tract population identifying as Black greater than 20% [66% decline in IRR, 95% CI (54%, 75%)]. % census tract population identifying as Hispanic < 5% [67% decline in IRR, 95% CI (60%, 72%)], % census tract population identifying as Hispanic between 5% and 10% [68% decline in IRR, 95% CI (52%, 79%)], % census tract population identifying as Hispanic between 10% and 20% [68% decline in IRR, 95% CI (57%, 76%)], % census tract population identifying as Hispanic greater than 20% [63% decline in IRR, 95% CI (53%, 71%)]. % census tract population identifying as below the FPL < 5% [67% decline in IRR, 95% CI (56%, 75%)], % census tract population identifying as below the FPL between 5% and 10% [69% decline in IRR, 95% CI (59%, 76%)], % census tract population identifying as below the FPL between 10% and 20% [62% decline in IRR, 95% CI (52%, 69%)], % census tract population identifying as below the FPL greater than 20% [70% decline in IRR, 95% CI (58%, 79%)]. Changes in incidence rate ratios for individuals who identify between the ages of 27-39 were not statistically significant.

Significant declines in CIN +2 incidence rate ratios for the total population were found in women in the following age groups: age 21 [85% decline in IRR, 95% CI (78%, 89%)], age 22 [81% decline in IRR, 95% CI (71%, 87%)], age 23 [75% decline in IRR, 95% CI (67%, 81%)], age 24 [60% decline in IRR, 95% CI (47%, 70%)], age 25 [44% decline in IRR, 95% CI (27%, 57%)], and age 26 [35% decline in IRR, 95% CI (10%, 54%)] (see figure 8). Change point analysis show that declines in incidence of CIN +2 cases in age group 21-22 begin in 2010 (i.e. 3rd year of surveillance period). Declines in incidence rate of CIN 2+ in age group 23-25 begin in 2012 (i.e. 4th year of data collection). Declines in individuals age 26 are predicted to begin in 2011 (i.e. 3rd year of data collection). Changes in incidence rate ratios for individuals who identify between the ages of 27-39 were not statistically significant.

When incidence rates were estimated among the screened population, significance in CIN +2 incidence rate declines held only in individuals ages 21-25 (see figure 9). When adjusted by BRFSS data the following declines in CIN +2 incidence rate ratios were observed: age 21 [80% decline in IRR, 95% CI (72%, 85%)], age 22 [74% decline in IRR, 95% CI (65%, 81%)], age 23 [66% decline in IRR, 95% CI (54%, 75%)], age 24 [46% decline in IRR, 95% CI (29%, 59%)], and age 25 [30% decline in IRR, 95% CI (1%, 50%)]. Change point analysis predict onset of incidence rate declines in each age group at the following time points: age 21 (year 2 – 2010), age 22 (year 2 – 2010), age 23 (year 4 – 2012), age 24 (year 4 – 2012), age 25 (year 7 – 2015).

Figure 8: CIN 2+ Incidence Rate Trends – Total Population – U.S. Census Tract Data

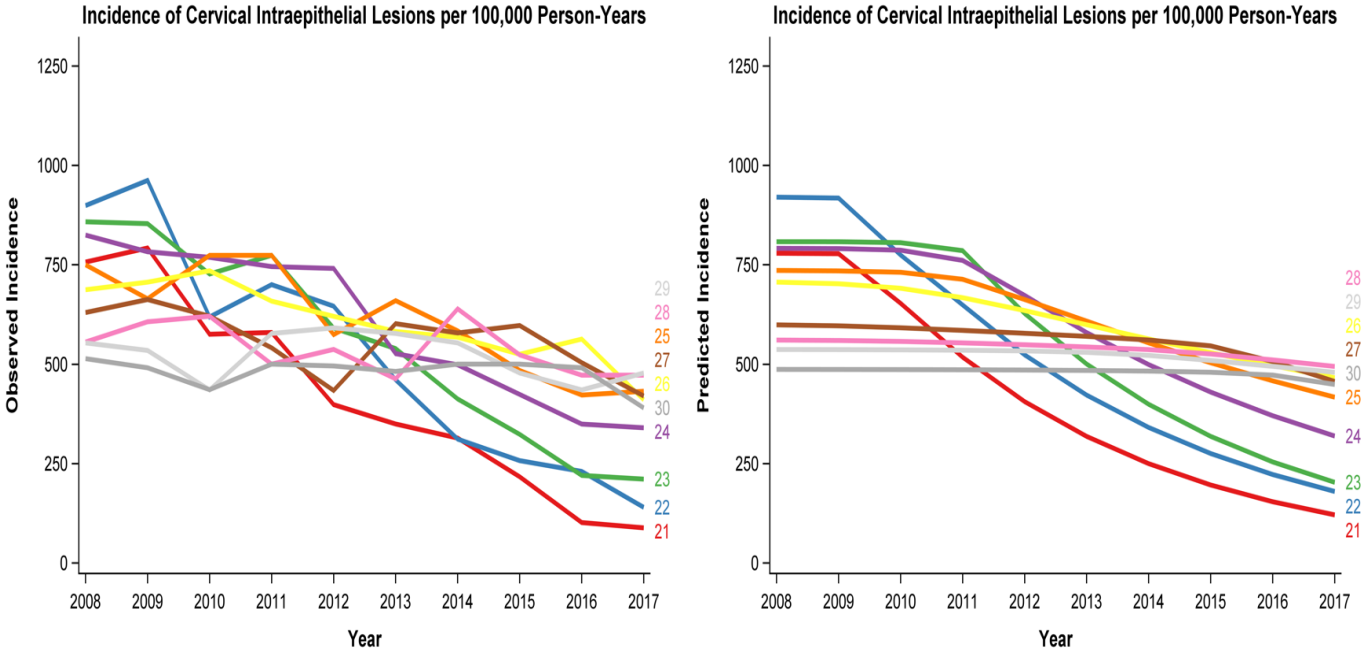
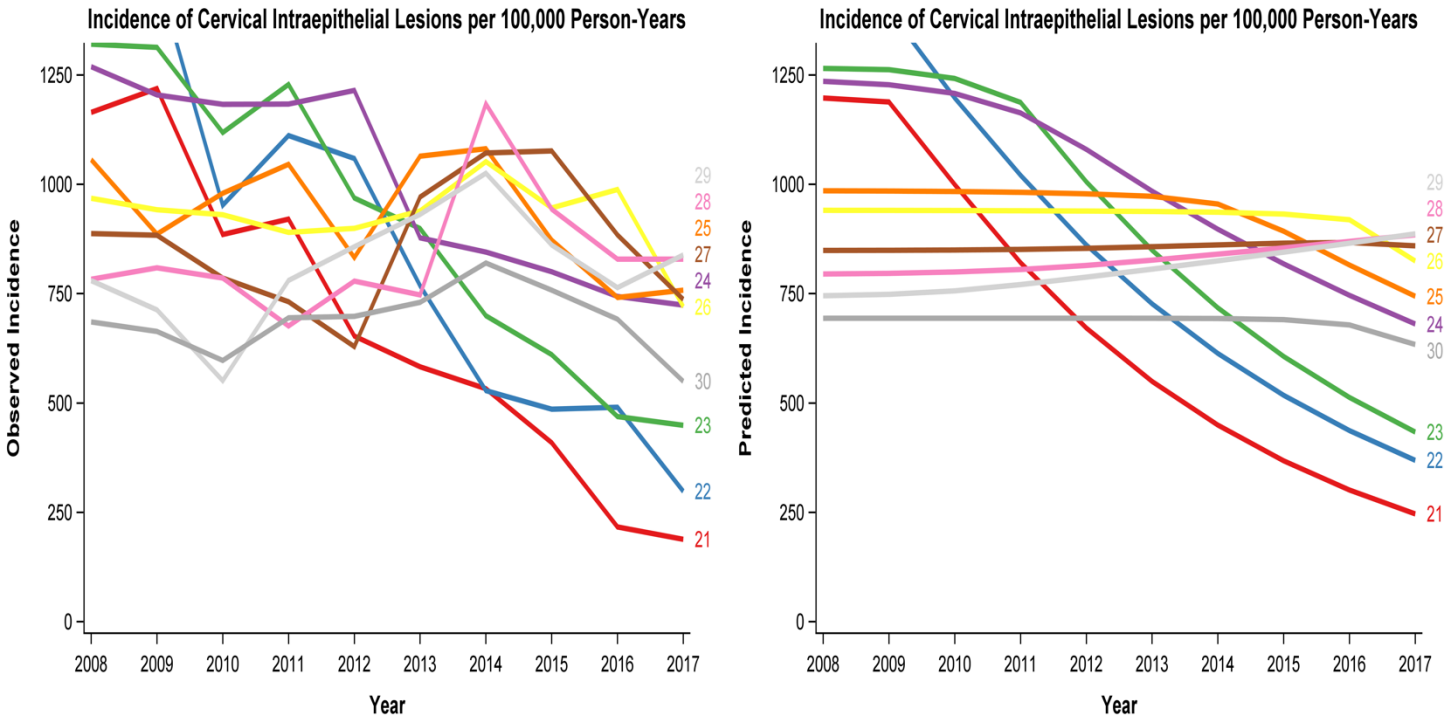


Figure 9: CIN 2+ Incidence Rate Trends – Screening Population – BRFSS Data



Discussion

Our results showed a statistically significant decline in incidence rate per 100,000 person-years of cervical intraepithelial neoplasia diagnoses of grade 2 or higher in individuals age 21-26 from 2008-2017. When incidence rates were estimated among the screened population, incidence rate declines remained statistically significant for individuals ages 21-25.

When incidence rates of CIN 2+ are stratified by race, ethnicity, and socioeconomic status these declines are shown to be statistically significant in the age group 21-24 across all levels of each variables. Statistically significant declines were observed regardless of the percentage of the population in a given census tract that identified with each sociodemographic variable (i.e. $< 5\%$, $\geq 5\%$ and $< 10\%$, $\geq 10\%$ and $< 20\%$, and $\geq 20\%$). The presence of declines of CIN 2+ incidence in areas with varying population sizes of Latina women, Black women, and women living below the poverty lines suggests that all three sociodemographic communities are showing similar declines since introduction of HPV vaccination in 2006. Additionally, older age cohorts (i.e. 25-

29, 30-34, and 35-39) also display declines in CIN +2 incidence rates across racial and socioeconomic identities. However, these declines are only observed in census tracts where less than 10% of individuals identify as Black, Latinx, or below the federal poverty line and they are not statistically significant based on current data.

In the oldest age cohort (i.e. 35-39 yr-olds) observed and predicted incidence rate trends revealed that incidence of CIN 2+ was increasing in census tracts where more than 10% of individuals identified as Black, Latinx, or below the federal poverty line. This may be attributable to a variety of reasons. For example, these census tracts may be seeing an expansion of healthcare services in succeeding years, thereby allowing more women to undergo cervical cancer screenings which would identify these precancerous lesions. These older women would also have been outside of the age group for which the HPV vaccination schedule was originally recommended, even when looking back to 2006 when they were between the ages of 24-28. Alternatively, these rising trends may be attributable to behavioral changes (e.g. changes in sexual behavior) centralized in these census tracts. Future field research, medical history collection of cases, and longitudinal follow-up will be necessary to identify risk factors for these trends.

This same time period saw vaccine coverage for adolescent youth ages 13-15 in Connecticut fluctuate between 25.8% and 47.1% according to the National Immunization Survey – Teens [16] reported by the CDC. Rising trends in HPV coverage in adolescents in CT should lead to substantial declines in CIN +2 diagnoses in older age groups in succeeding years.

The strength of this analysis is that population level trends provide information on the direct impact of HPV vaccination and the indirect effect of herd immunity. The continued decline of CIN +2 incidence rate trends among the screened populations indicates that the decrease in precancerous cervical lesions cannot be adequately explained by changes in clinical guidelines

which now recommend more infrequent cervical cancer screenings for cost-effective reasons in women below 30 (i.e. every 3 years instead of annually).

However, this analysis should be acknowledged with several limitations. As an ecological study this analysis is limited to the population level variables available in the data collected through HPV-IMPACT. Data collection did not account for individual level information regarding whether or not cases were previously vaccinated for HPV. Moreover, BRFSS data was only provided biannually and was collected through self-report. In other words, women who may have gone to a primary care clinician or gynecologist may have mistaken other gynecological procedures for a Pap smear and mistakenly reported yes to having undergone a Pap smear in the past year. This would result in an overestimation of the denominator multiplier and underestimation of CIN 2+ incidence rates. That said, a benefit of self-report data is that it can account for cases not identifiable through insurance claims data, such as undocumented women who may undergo cervical cancer screenings at free clinics without traceable claims data to confirm the procedure. Lastly, this data does not discern between cisgender women and transgender men or gender non-conforming individuals, thereby leaving room for missing data from key demographics.

This analysis contributes to growing literature assessing the impact of HPV vaccination coverage on the incidence of HPV related sequalae, including anogenital warts, pre-cancerous lesions, and cervical cancer with a special focus on trends by area-based measures of sociodemographic characteristics. Continued longitudinal analysis should be performed to assess if CIN + 2 diagnoses decline in older age groups and to advocate for further HPV vaccination campaigns.

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